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Critical Review

Involved Site Radiation Therapy in Adult Lymphomas: An Overview of International Lymphoma Radiation Oncology Group Guidelines

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Involved node radiation therapy for lymphoma was introduced with the aim of using the smallest effective treatment volume, individualized to the patient's disease distribution, to avoid the potentially unnecessary normal tissue exposure and toxicity risks associated with traditional involved field radiation therapy. The successful implementation of involved node radiation therapy requires optimal imaging and precise coregistration of baseline imaging with the radiation therapy planning computed tomography scan. Limitations of baseline imaging, changes in patient position, and anatomic changes after chemotherapy may make this difficult in routine practice. Involved site radiation therapy (ISRT) was introduced by the International Lymphoma Radiation Oncology Group as a slightly larger treated volume, intended to allow for commonly encountered uncertainties. In addition to imaging considerations, the optimal ISRT treatment volume also depends on disease histology, stage, nodal or extranodal location, and the type and efficacy of systemic therapy, which in turn influence the distribution of macroscopic and potential subclinical disease. This article presents a systematic overview of ISRT, updating key evidence and highlighting differences in the application of ISRT across the lymphoma clinical spectrum.

Introduction

The involved node radiation therapy (INRT) concept for early stage Hodgkin lymphoma (ESHL) was introduced by the European Organisation for Research and Treatment of Cancer (EORTC) in 2006.[1] The intent was to use the smallest effective treatment volume, individualized to the patient's disease distribution, avoiding the potentially unnecessary normal tissue exposure and toxicity risks associated with standard involved field radiation therapy (IFRT).[1,2] For ESHL, the smallest effective volume was considered to include only disease sites evident at diagnosis, assuming the ability of chemotherapy to control adjacent potential microscopic disease. The efficacy of INRT for ESHL was subsequently confirmed in a prospective randomized trial.[3]

To apply this "smallest effective volume" principle more broadly in lymphoma practice, 2 key considerations needed to be addressed. First, small irradiated volumes require optimal imaging for accurate disease localization, as well as precise coregistration of baseline imaging information with the RT planning computed tomography (CT).[4,5] In practice, baseline imaging may be suboptimal or difficult to translate to the planning CT, owing to altered patient position or anatomic changes after chemotherapy. In 2014, the International Lymphoma Radiation Oncology Group (ILROG) introduced involved site radiation therapy (ISRT), a slightly larger volume intended to allow for these commonly encountered uncertainties.[6]

Second, it was recognized that the smallest effective volume may "look different" in different clinical settings. Histology, stage, nodal or extranodal location, and the type and efficacy of systemic therapy all affect the distribution of macroscopic and potential subclinical disease, which in turn determine the optimal ISRT volume. ILROG has published guidelines for ISRT in different clinical settings, and ISRT is internationally recognized as the standard of care for malignant lymphoma.[6-15]

The present article provides a systematic overview of ISRT, updating key evidence and highlighting differences in the application of ISRT across the lymphoma clinical spectrum (previous ILROG guidelines may be consulted for additional details). Commonly encountered challenges in implementation will be discussed.

Imaging Considerations

Accurate contouring requires a thorough clinical assessment, high-quality imaging, and sometimes supplementary tests (eg, endoscopy).[5,16] 18-Fluorodeoxyglucose (FDG) positron emission tomography (PET) is critical for accurate staging and may modify RT volumes.[17-25] PET does not obviate the need for contrast CT to delineate (for example) mediastinal lymphadenopathy, or magnetic resonance imaging (MRI) to define head and neck involvement. Small-volume disease not evident on PET may be visible on CT or MRI.[5,16]

Imaging uncertainties may be due to the following factors (Fig. 1):

A. Suboptimal baseline imaging
   1. An incomplete study (eg, omitting the neck from a CT)
   2. CT performed without contrast
   3. Failure to perform MRI when indicated
   4. FDG uptake in brown fat obscuring small-volume disease
   5. Prior steroid exposure compromising PET interpretation

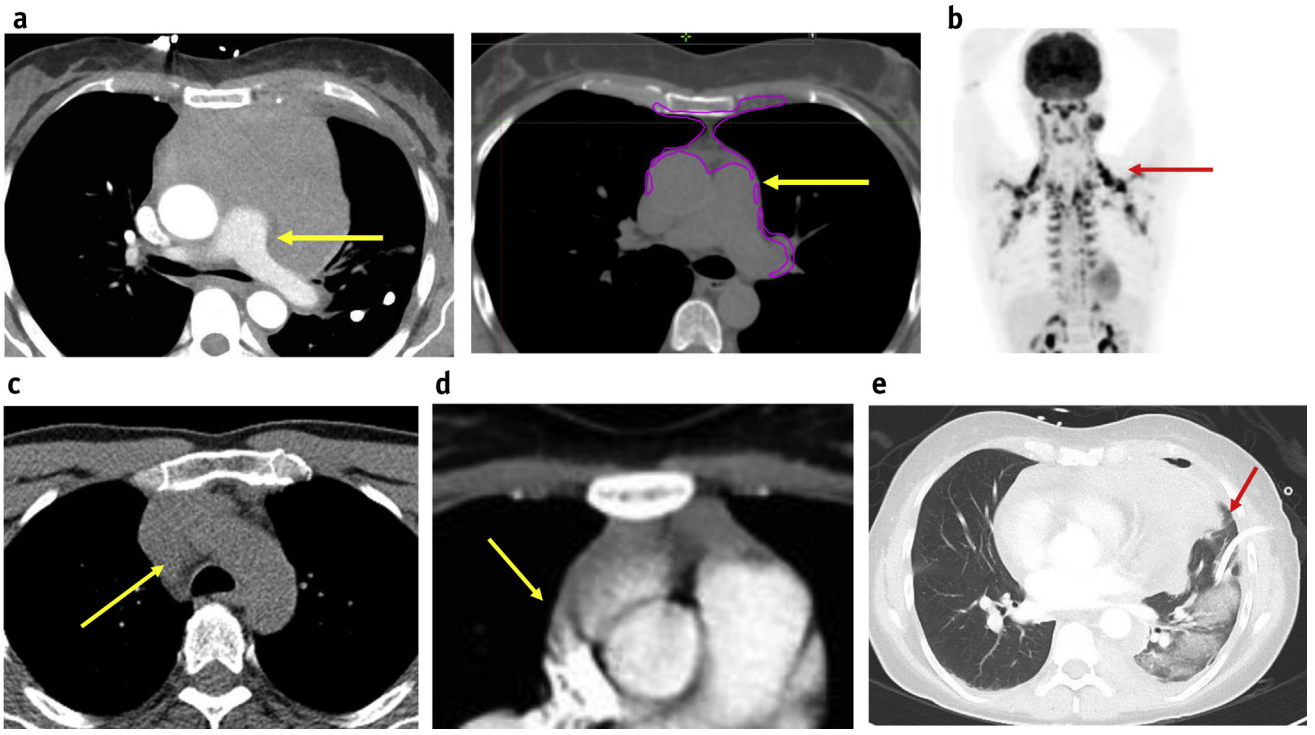


Fig. 1. Imaging uncertainties: (a) anatomic shifts after chemotherapy (note the shift of the aorta and pulmonary artery); (b) brown fat potentially obscuring disease; (c) poor anatomic definition with noncontrast computed tomography; (d) ill-defined extent of pericardial infiltration; (e) uncertainty whether lung is displaced or infiltrated.

Where possible, suboptimal studies should be repeated before commencing systemic therapy (eg, repeating a PET scan after administration of beta-blockers to reduce brown fat uptake).[26]

B. Difficult imaging interpretation

1. Equivocal nodes near definite disease sites (eg, equivocal FDG uptake in nonenlarged nodes)
2. Defining the extent of pleural or pericardial tumor infiltration
3. Distinguishing organ displacement from infiltration (eg, lung atelectasis vs tumor infiltration)
4. Heterogeneous FDG avidity.[5,18]

C. Patient position and set-up

Ideally, baseline imaging is performed in the intended treatment position to facilitate accurate image fusion.[4] This may not always occur. For example, optimal PET imaging may require arms to be elevated, whereas treating female patients with arms down may reduce the volume of breast tissue in the plane of treatment (Fig. 2).[27] Differences in arm or neck position at baseline and planning CT, and deep inspiration breath hold may complicate clinical target volume (CTV) localization (Fig. 3).

D. Anatomic shifts after systemic therapy

After systemic therapy, regression of bulky mediastinal or abdominal lymphomas may alter the position and shape of normal structures (Fig. 1a).

PET and structural imaging should always be reviewed with a PET physician/radiologist.[18] In the presence of imaging uncertainties, an additional radial and craniocaudal expansion may be added to the CTV to ensure adequate tumor coverage. The expansion should be determined on an individual case basis after systematically comparing anatomic landmarks in the staging and planning scans, correlating baseline tumor location with the anatomy after systemic therapy.[28,29] Determination of the CTV requires clinical judgment and consideration of radiologic uncertainties and toxicity risks.[6,9,11]

Benefits and Risks of Reduced Irradiated Volumes

The shift from mantle RT to IFRT substantially reduced breast cancer risk.[30,31] The shift from IFRT to ISRT is anticipated to further reduce late toxicity risk, based on dosimetric and modeling studies.[32-43] However, small treatment volumes are subject to a degree of anatomic uncertainty, and inadequate tumor coverage may increase relapse risk.[29,44-48] With optimal imaging and guidelines, the systematic delineation uncertainty appears to be comparable to that reported in other tumor types.[47] ISRT requires accurate treatment delivery and verification (Fig. 4).

In every case, adequate tumor coverage must be balanced against the late toxicity risks of the requisite

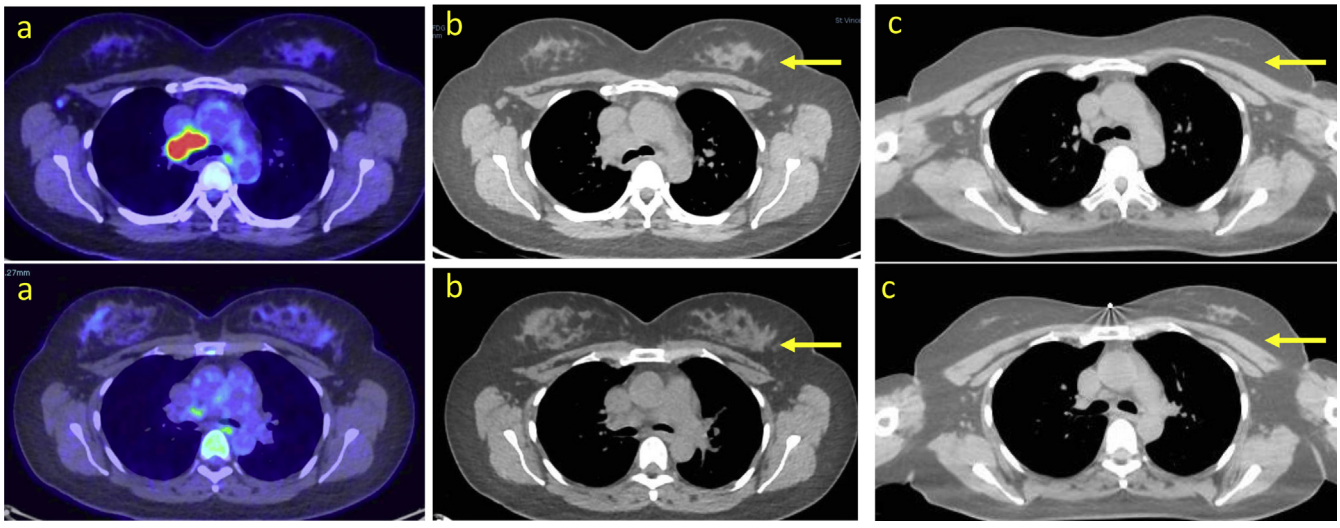
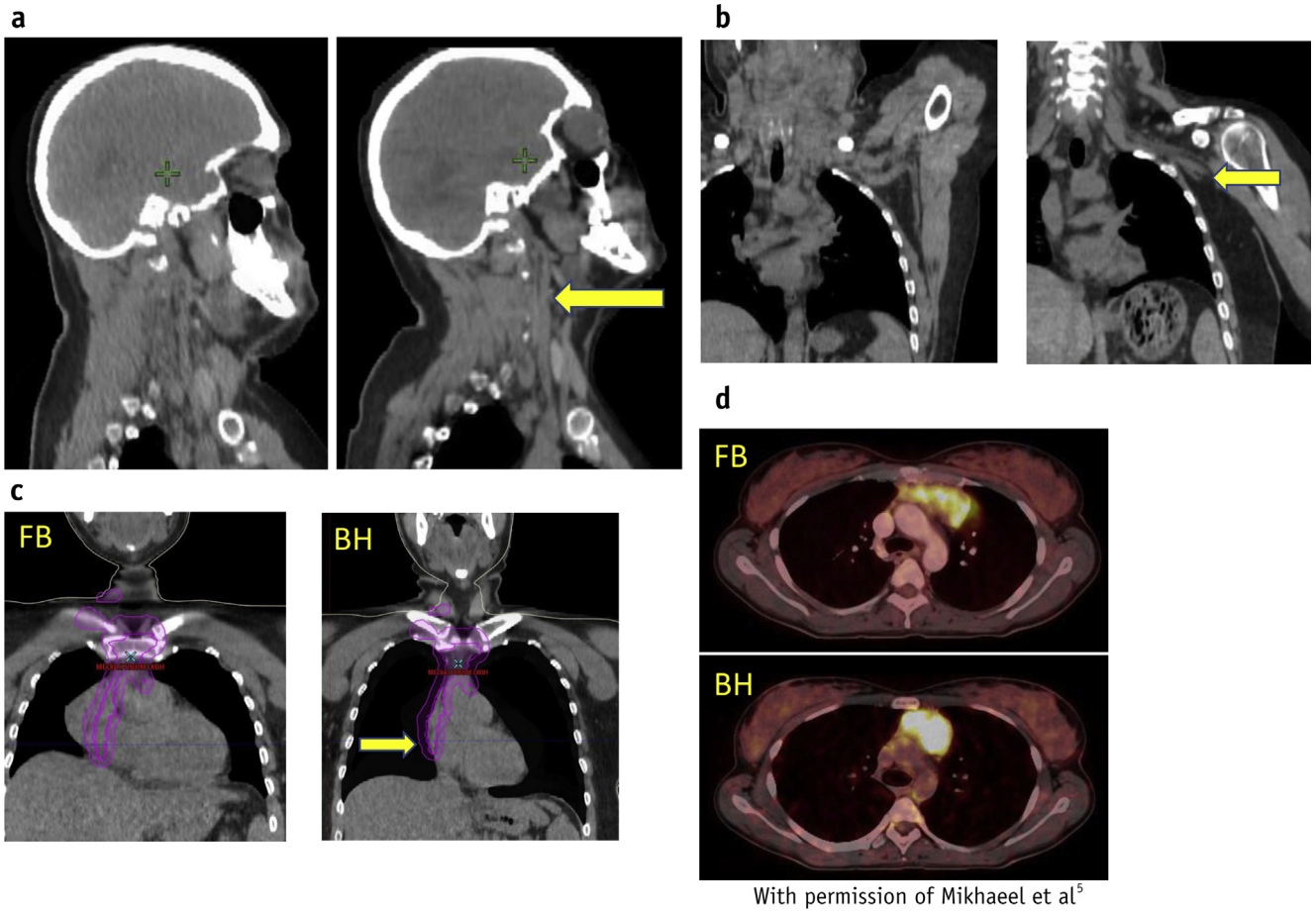


Fig. 2. Effect of arm position: (a) baseline positron emission tomography; (b) diagnostic computed tomography; (c) corresponding levels on planning computed tomography with arms down. Arrows highlight reduced breast volume at relevant planes.



With permission of Mikhaeel et al[5]

Fig. 3. Impact of treatment position: (a) altered neck position changes relationship of nodes and pharyngeal soft tissue to bony landmarks; (b) arm position alters the relationship of cervical and pectoral lymph nodes to bony and soft tissue landmarks; (c) heart and mediastinal structures in breath-hold (BH) and free-breathing (FB); (d) positron emission tomography/computed tomography illustrates blurring and widening of a mediastinal mass in FB.

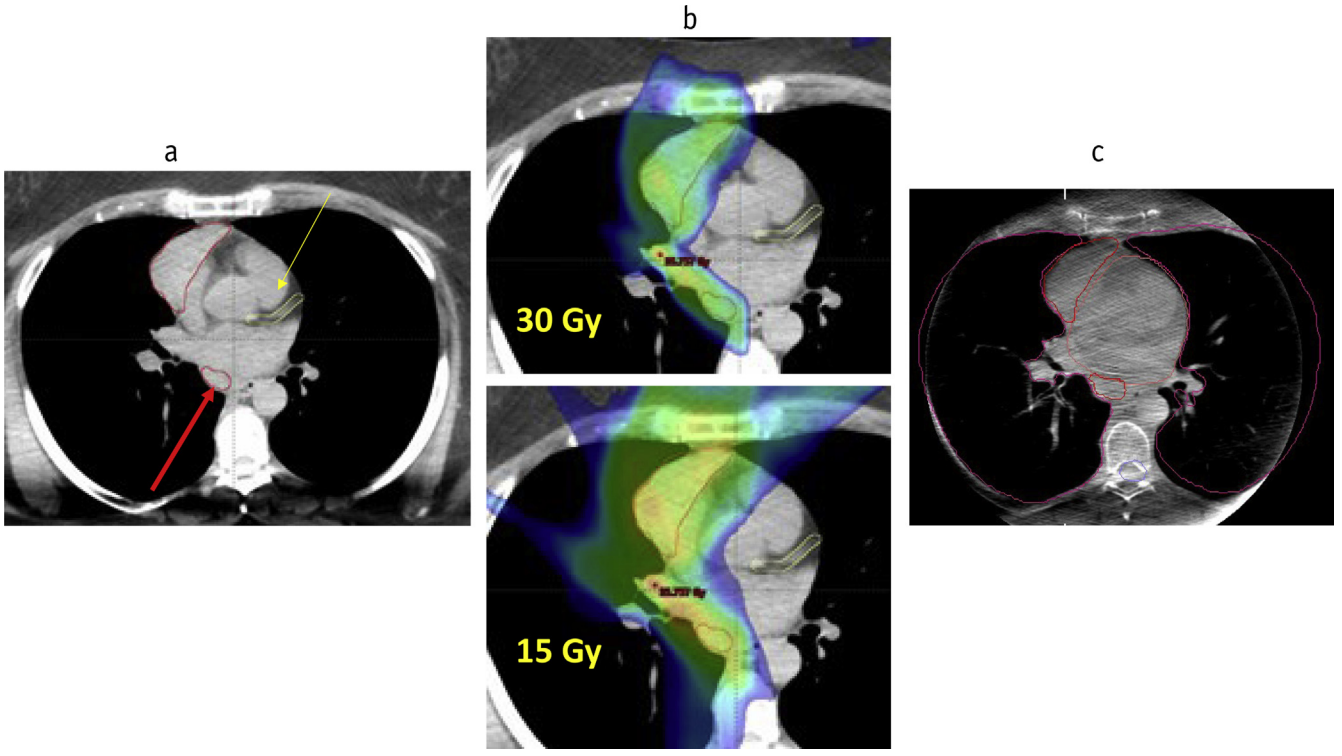


Fig. 4. Treatment verification: (a) clinical target volume contours (red arrow) and coronary artery (yellow arrow); (b) intensity modulated radiation therapy plan showing tight coverage of the involved site radiation therapy volume avoiding coronary artery; (c) cone beam computed tomography confirms accurate delivery. (A color version of this figure is available at https://doi.org/10.1016/j.ijrobp.2020.03.019.)

treatment volume. Acceptable toxicity risks are influenced by the magnitude of benefit anticipated from RT, patient age (ie, the likelihood of experiencing late toxicity), and alternative management options, including potential salvage therapy. Importantly, the toxicity risk reduction associated with smaller treated volumes depends on tumor location and patient demography. Small reductions in mediastinal treatment volumes may significantly reduce exposure of cardiac substructures, such as the coronary arteries, whereas small changes in the treated volume in, for example, the inguinal region of an older patient may only modestly affect toxicity.

In clinical settings for which published volume and dose data are limited, the following guidelines may indicate a range of potentially acceptable volume (or dose) recommendations. In such settings, volume and dose decisions should reflect uncertainties of disease localization and toxicity considerations in each case.

RT dose constraints used for common epithelial malignancies are less relevant in the lymphoma setting; the prescribed doses are often lower than the conventional constraints, and important late toxicities may occur even after low doses in long-term survivors. Suggested dose constraints for patients with mediastinal lymphoma are shown in Table 1.[49] Dose constraints should be applied with flexibility. Some clinical settings necessitate a treatment plan that does not meet ideal dose constraints. In settings where standard dose constraints are easily achieved, further plan optimization may be appropriate to keep critical organ doses as low as reasonably achievable. Ideally, flexible dose-planning tools will allow optimization of the trade-off between recurrence risk and late effects risk, and RT plan optimization and decision analysis tools for lymphomas continue to be developed.[50,51]

Terminology

The following definitions will be used, reflecting International Commission on Radiation Units guidelines.[52,53]

Gross tumor volume (GTV): the "gross demonstrable extent and location of the tumor," including radiologically evident (generally PET positive) lesions present at diagnosis in patients treated with RT alone. Using combined modality therapy, the "prechemo" GTV denotes evident lesions before systemic treatment, whereas the "postchemo" GTV denotes radiologically evident or biopsy-proven disease sites after systemic therapy.

CTV: the GTV and/or a volume containing "subclinical malignant disease with a certain probability of occurrence considered relevant for therapy." For treatment with RT alone, this volume includes the GTV and adjacent lymph nodes. For combined-modality therapy, it includes any "postchemo" GTV as well as the tissue volume that contained initially involved lymph nodes and sites of infiltrative disease (ie, the "prechemo" GTV) that may have

Table 1 Dose and volume considerations

	Optimal*	Acceptable†	If necessary‡	Avoid
Heart (89, 145, 146)				
Mean (Gy)	<5	5-10	10-18	Coronary arteries and left ventricle
V15	<10%	10%-25%	25%-35%	
V30		<15%	15%-20%	
Lung (147)				
V5	<35%	35%-45%	45%-55%	
V20	<20%	20%-28%	28%-35%	
Mean (Gy)	<8	8-12	12-15	
Thyroid (148)				
V25	<62.5%			Whole thyroid
Breast				
Mean (Gy)	<4	4-15	>15	Glandular tissue
V4	<10%	10%-20%	>20%	
V10		<10%	>10%	

* For favorable disease, small-volume early stage lymphoma.
† For bulky mediastinal disease.
‡ Relapse/refractory disease setting. Adapted with permission from Dabaja et al.[49]

become PET negative or normalized on structural imaging after systemic therapy. In specific clinical settings, the CTV also includes sites considered to be at particular risk based on knowledge of the natural history and patterns of spread.

Equivocal nodes: lymph nodes near definite disease sites that are enlarged (>1 cm) but PET negative; normal in size with equivocal FDG uptake; or present in an increased number or with asymmetrical distribution. The decision to include equivocal nodes in the GTV or CTV depends on clinical context.

The internal target volume (ITV) and planning target volume (PTV) should be determined according to institutional practice.

Clinical Scenarios

The ISRT volume may be considered in 5 broad clinical groups:

1. Early stage indolent non-Hodgkin lymphoma (NHL) and nodular lymphocyte-predominant HL (NLPHL) treated with RT alone: The CTV includes all evident sites plus an adequate volume to encompass potential adjacent subclinical disease.
2. ESHL and diffuse large B-cell lymphoma (DLBCL) after limited systemic therapy: Systemic therapy is highly likely to control subclinical disease, so the CTV may be strictly limited to disease sites evident at diagnosis (which are at highest risk of residual microscopic disease).
3. Primary extranodal lymphoma: The CTV is usually the entire involved organ (with some exceptions) because extranodal lymphomas often display an infiltrating or multifocal pattern.
4. Advanced stage HL or aggressive NHL after a full course (typically 6 cycles) of systemic therapy: The CTV includes any residual GTV plus a subset of disease sites at elevated risk of harboring subclinical disease after systemic therapy.
5. Relapsed lymphoma undergoing salvage therapy with or without transplantation: The CTV includes some or all relapse sites and selected sites of prior disease involvement

Early stage indolent nodal lymphoma treated with RT alone

Overview

Historically IFRT was used as sole treatment for localized follicular lymphoma (FL), nodal marginal zone lymphoma (MZL), and NLPHL.[54-62] Typically, ISRT volumes include radiologically evident disease sites plus an expansion to encompass potential adjacent microscopic disease sites.[9]

Key evidence

Evidence for the efficacy of fields smaller than IFRT for FL is provided in several publications.[54,55,63] Retrospective studies from Vancouver and Stanford reported excellent locoregional control using field margins up to 5 cm and 3 to 6 cm, respectively.[54,55] Smaller margins are commonly used in routine practice. Emerging data suggest that similar treated volumes may also be effective for NLPHL.[62-64]

Volume

The GTV includes PET-positive nodes and should be extended to include nearby enlarged or equivocal nodes, particularly if disease demonstrates low FDG avidity (Fig. 5).

The CTV includes the GTV, with consideration given to including adjacent visible nodes (even if not enlarged). The CTV may extend to the boundaries of the involved nodal compartment in the axial plane, as well as several centimeters in the craniocaudal plane, depending on radiologic uncertainties (Fig. 6). For sites in proximity to sensitive structures (eg, salivary glands, breast in younger patients) a minimal CTV expansion may be used to reduce morbidity risk.

Although not now routine, larger volumes (approximating IFRT) may be considered when imaging is not optimal.

Dose

For FL, 24 to 30 Gy is recommended, with a randomized trial suggesting the equivalence of 24 Gy to higher doses used historically.[14,54,55,65-67]

For NLPHL, 30 Gy is recommended.[60,61,64]

ESHL and DLBCL after Limited Systemic Therapy

Hodgkin lymphoma

Key evidence

The EORTC H10 trial confirmed the efficacy of INRT after 3 cycles of adriamycin, bleomycin, vinblastine, dacarbazine (ABVD) for favorable ESHL, with results comparable to those seen with the use of IFRT in the RAPID and EORTC H7 trials.[3,68,69] INRT (after 4 cycles of ABVD) for unfavorable ESHL produced a smaller benefit than in the favorable cohort, with an apparently higher locoregional failure rate.[3]

After 2 cycles of ABVD for German Hodgkin Study Group (GHSG) favorable ESHL, IFRT is effective, although ISRT has not been evaluated in a large prospective study in this setting.[70] It is uncertain whether 2 cycles of ABVD reliably control subclinical disease in nodes within an IFRT volume but beyond an ISRT volume. A small US study provides support for the efficacy of ISRT, with a reported 4-year RFS of 93%.[71]

GHSG HD14 utilized IFRT after 2 escalated bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, prednisolone (escBEACOPP) plus 2 ABVD for unfavorable ESHL.[72] ISRT is not anticipated to be less effective in this setting than after 4 ABVD. GHSG HD17 addresses the role of INRT for interim PET-positive patients.

For patients who remained PET positive (Deauville score $\geq$3) after 2 to 3 cycles of ABVD, IFRT produced a nearly 90% 5-year progression-free survival (PFS) in both GHSG HD16 and the UK RAPID trials.[68,73] For PET-positive patients (Deauville score $\geq$3) after 2 ABVD in the EORTC H10 trial, INRT was associated with a 5-year PFS of 77% and 91% after further ABVD or escBEACOPP, respectively (most had unfavorable disease).[3]

Volume

For patients in metabolic complete response (CR) after chemotherapy, the CTV includes locations of initially

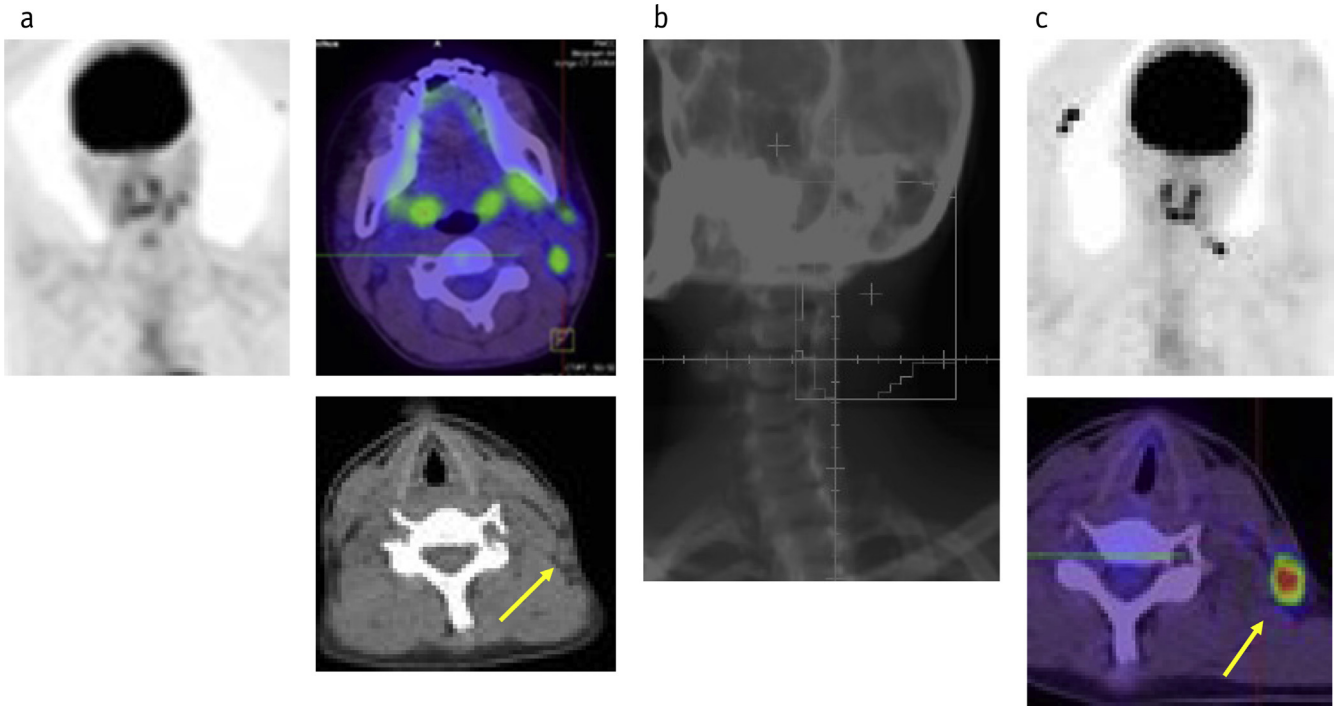


Fig. 5. Stage I nodular lymphocyte predominant Hodgkin lymphoma treated with involved site radiation therapy (ISRT) alone: (a) positron emission tomography (PET) positive upper neck node and PET negative lower neck node (arrow); (b) ISRT upper neck field; (c) relapse in unirradiated lower neck node. Include equivocal nodes in ISRT volume for indolent lymphomas treated with radiation therapy alone.

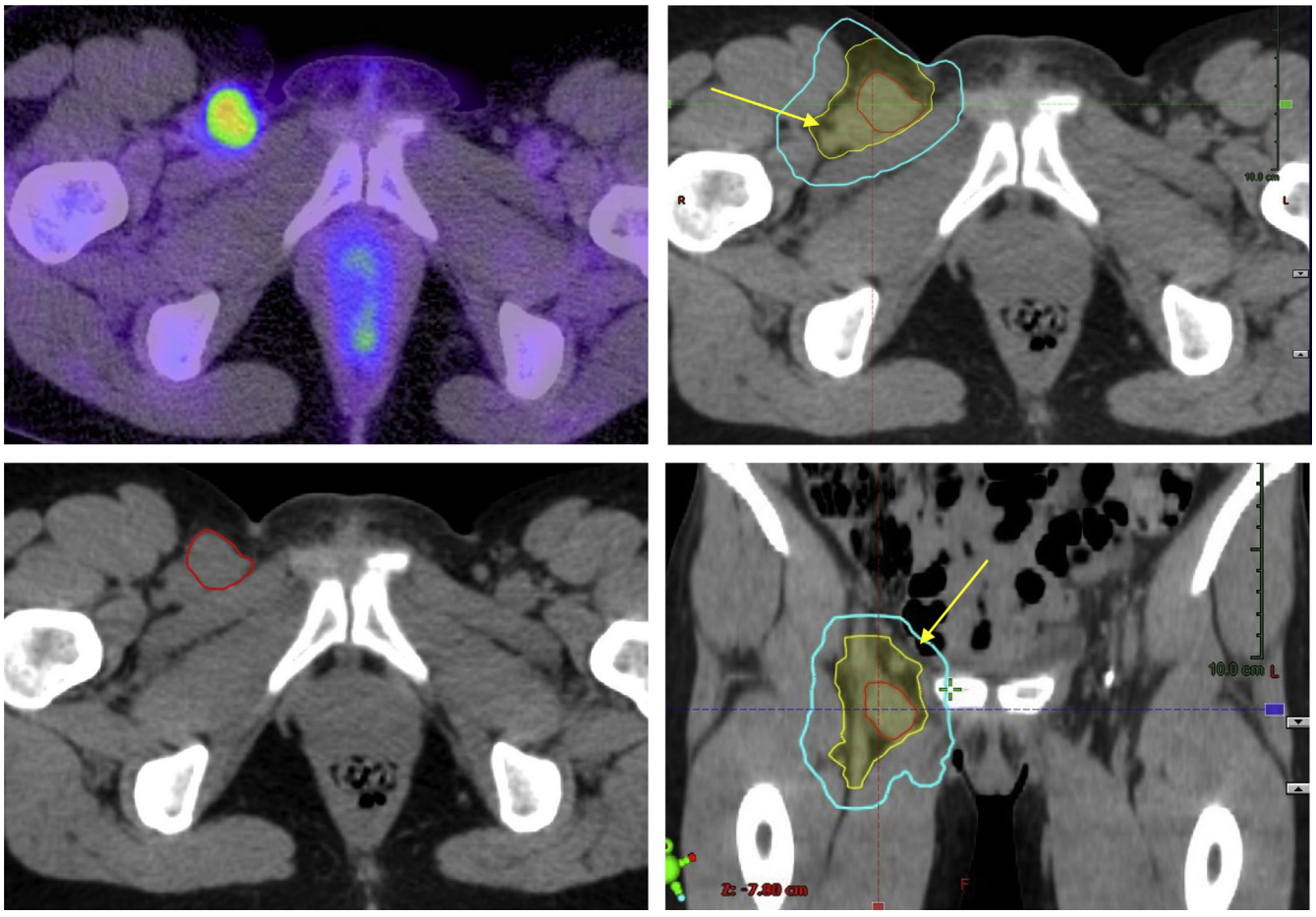


Fig. 6. Stage I follicular lymphoma: gross tumor volume (red) encompasses positron emission tomography positive disease; CTV (yellow) includes adjacent, positron emission tomography negative nodes (arrows) and extends to anatomic boundaries. (A color version of this figure is available at https://doi.org/10.1016/j.ijrobp.2020.03.019.)

involved nodes, including nodes that have normalized after systemic therapy (Fig. 7). Widely separated initially involved sites may be treated separately, and it is not necessary to irradiate the intervening (initially uninvolved) tissue.

The CTV reflects the original craniocaudal disease extent. In the axial plane, the CTV is adjusted for tumor shrinkage to avoid unnecessary irradiation of initially displaced, uninvolved tissue. If the lymphoma infiltrates an adjacent organ (typically lung or chest wall), then the initially infiltrated tissue volume should be included in the CTV, with consideration of the toxicity implications of the larger volume.

Contiguous initially equivocal nodes should be considered for inclusion in the CTV, but the CTV should not be enlarged to include initially normal nodes.

For GHSG favorable disease, ISRT is increasingly used after 2 cycles of ABVD. Because data supporting this practice are still emerging, some authorities use a slightly more generous ISRT volume (as for indolent lymphoma treated with RT alone).

For patients who do not achieve a PET CR, the residual FDG-avid lesion constitutes the "postchemo" GTV. If this lesion occurs within a larger PET-negative mass, the entire mass evident on CT, along with initially involved sites, should be included in the CTV.

In this and later sections, it must be emphasized that patients with residual FDG avidity after systemic therapy for HL (or DLBCL) require careful multidisciplinary management. Although selected patients with limited residual FDG avidity may be treated with RT alone, fit patients with extensive or progressive FDG-avid sites or biopsy-proven residual disease commonly proceed to salvage therapy and stem cell transplantation (see the *ISRT for relapsed/refractory aggressive NHL or HL* section).

Dose

For EORTC favorable ESHL in metabolic CR after 3 to 4 cycles of ABVD, 30 Gy is the standard dose (ESMO guidelines suggest 20 Gy).[3,13,68,72,74] For GHSG favorable disease, 20 Gy is standard after 2 cycles of ABVD.[70]

For residual PET-positive sites 36 to 40 Gy is recommended. Potential microscopic disease in surrounding FDG-negative masses (and initial sites in structural CR)

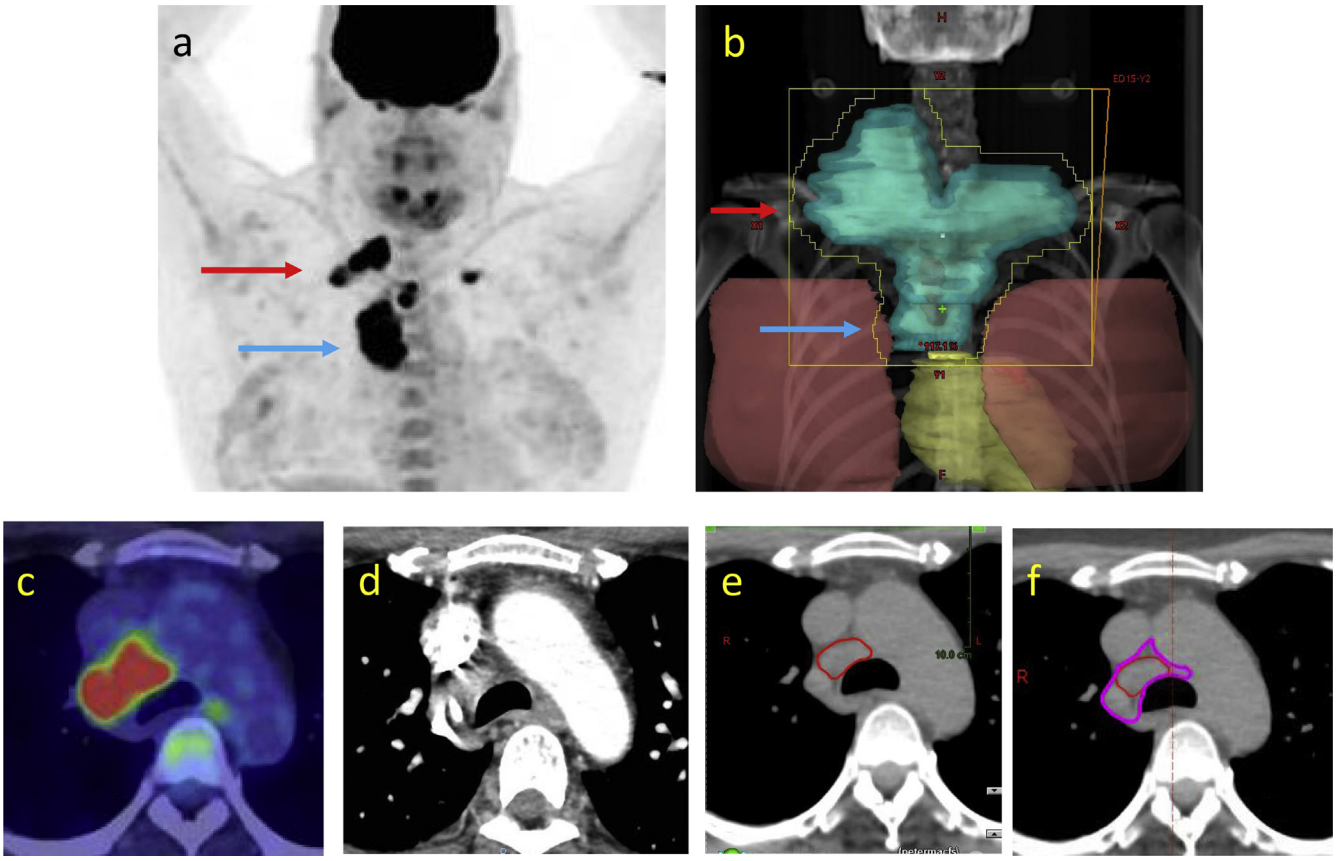


Fig. 7. Stage IIA classical Hodgkin lymphoma in positron emission tomography (PET) remission after 3 cycles of ABVD; (a) baseline PET, arms elevated; (b) treatment field on planning image, arms down; (c) baseline mediastinal nodes on PET; postchemotherapy residual mass on (d) contrast computed tomography; (e) planning CT; and (f) clinical target volume (CTV). Well-defined mediastinal anatomic boundaries allow precise CTV delineation (true involved-node radiation therapy), with generous supraclavicular CTV expansion allowing for anatomic changes due to altered arm position (involved site radiation therapy volume).

may be treated to 30 Gy to reduce potential toxicity (2 dose levels may be considered in other settings of residual PET positivity).

DLBCL

Key evidence

IFRT after 3 to 4 cycles of R-CHOP has been an established strategy for favorable stage I to II DLBCL.[75,76] Excellent results have been reported using modifications of ISRT (ie, margins of 1-5 cm on the GTV) in both retrospective and prospective nonrandomized studies.[77-83] A study comparing strict INRT with IFRT showed no difference in outcome.[82]

Volume

For patients in metabolic CR after chemotherapy, the CTV includes locations of initially involved nodes, including sites that have normalized after systemic therapy. Initial FDG avidity may be heterogeneous, sometimes due to the presence of necrotic tumor.[5] Contiguous nodes that were enlarged at diagnosis, but with low FDG avidity, should be included in the CTV when necrosis is suspected (Fig. 8). Contiguous initially equivocal nodes should be included in the CTV, but the CTV should not be enlarged to include initially normal nodes.

The CTV reflects the original craniocaudal disease extent. In the axial plane, the CTV is adjusted for tumor shrinkage to avoid unnecessary irradiation of initially uninvolved tissue displaced by tumor. If the lymphoma infiltrates an adjacent organ, the initially infiltrated tissue volume should be included in the CTV, with consideration of the toxicity implications of the larger volume.

For patients who do not achieve a PET CR, the residual FDG-avid lesion constitutes the "postchemo" GTV. If this lesion occurs within a larger PET-negative mass, the entire mass evident on CT, along with initially involved sites, should be included in the CTV.

Dose

Although a wide range of RT doses has been used after R-CHOP, a randomized trial suggests the equivalence of 30 Gy to higher doses.[67,76,83-86] The recommended dose for

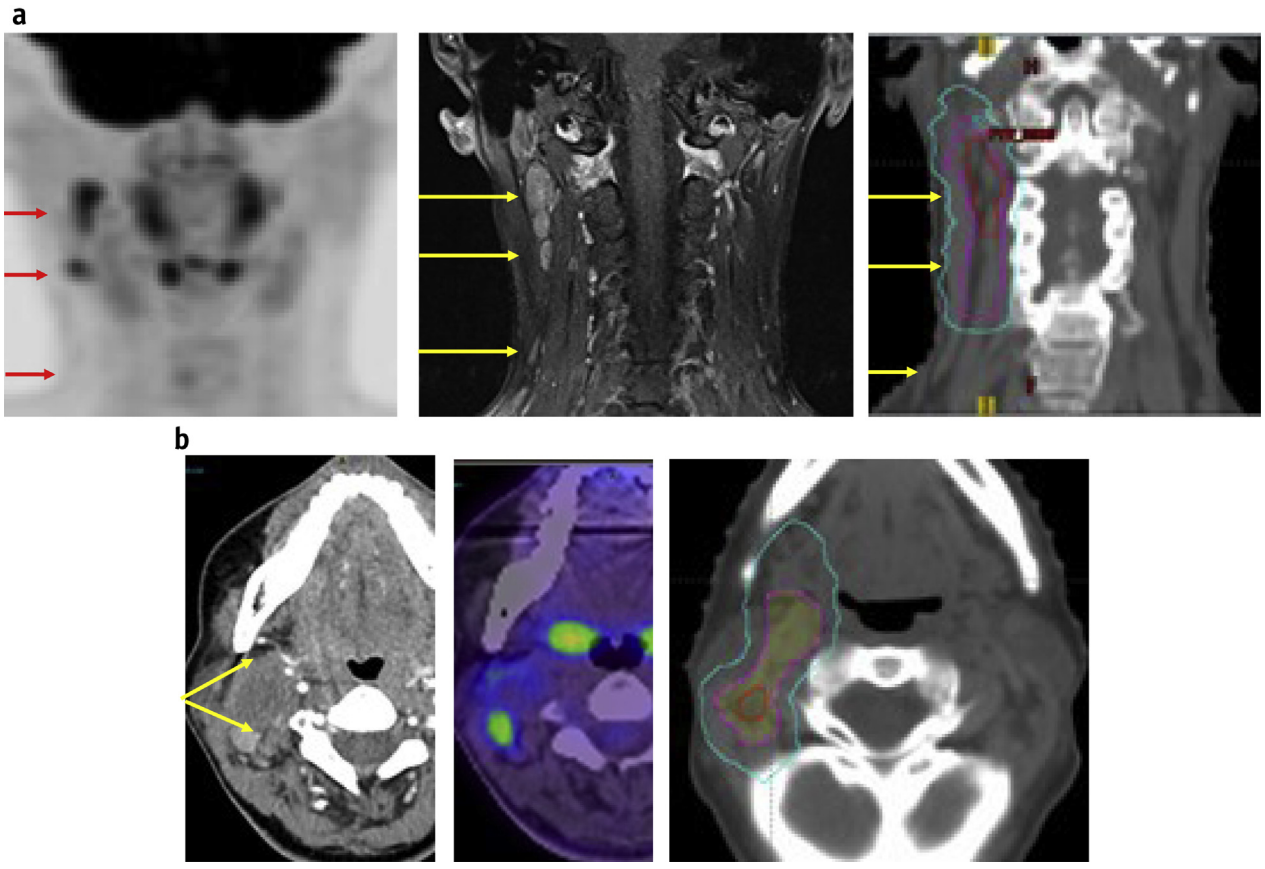


Fig. 8. Stage I diffuse large B-cell lymphoma treated with 3 cycles of R-CHOP and involved site radiation therapy: (a) Coronal positron emission tomography and magnetic resonance imaging demonstrate upper and midneck nodes. Lower right neck node is nonenlarged and fluorodeoxyglucose negative and excluded from the clinical target volume (CTV); (b) nodal mass is partly positron emission tomography negative (arrows) with ill-defined boundaries. The CTV includes all initially suspicious tissue.

sites in PET CR is 30 to 36 Gy. Lower doses are under evaluation.[83]

For low-risk, limited-stage DLBCL treated with 4 to 6 cycles of R-CHOP, limited PET-positive sites identified after 2 to 4 cycles should receive at least 36 to 40 Gy.[76,87,88]

Unfavorable Stage I to II Mediastinal Lymphoma: ESHL and Primary Mediastinal B-cell Lymphoma

Mediastinal lymphomas commonly occur in young patients for whom late toxicity considerations are important in determining the optimal use of RT. Although small-volume upper mediastinal lymphomas may often be safely irradiated, a bulky mass associated with contiguous lower mediastinum disease (Fig. 9a, 9b) or lung or chest wall infiltration may difficult to irradiate while respecting dose constraints for heart, lung, and breast (Table 1).[49] If advanced techniques (intensity modulated RT, volumetric modulated arc therapy, deep inspiration breath hold, or proton therapy) cannot facilitate the safe irradiation of the entire initial tumor volume, alternative approaches should be considered.

In such cases, a full course of systemic therapy may be given, with a "modified ISRT" volume limited to sites at greatest risk of relapse. Although rigorous patterns-of-failure data are lacking, many clinicians determine an ISRT volume based on sites of initial bulk, slow response (positive interim PET), and the presence of a residual mass. Potentially, this strategy may confer some of the benefit of standard ISRT while reducing normal tissue exposure and toxicity risk. Although it is assumed that potential small increases in the relapse rate will be more than offset by reductions in late toxicity, estimates of toxicity risk reduction are subject to uncertainty.[32,35] In addition, reduced RT-related toxicity may be offset in part by increasing anthracycline exposure of a full course of chemotherapy.[89] Clinical judgment is required to select the optimal treatment strategy in each case, recognizing these uncertainties; research is ongoing to develop quantitative methods to optimize management.

When disease is evenly distributed through multiple anatomic regions (neck, mediastinum, axillae), a large

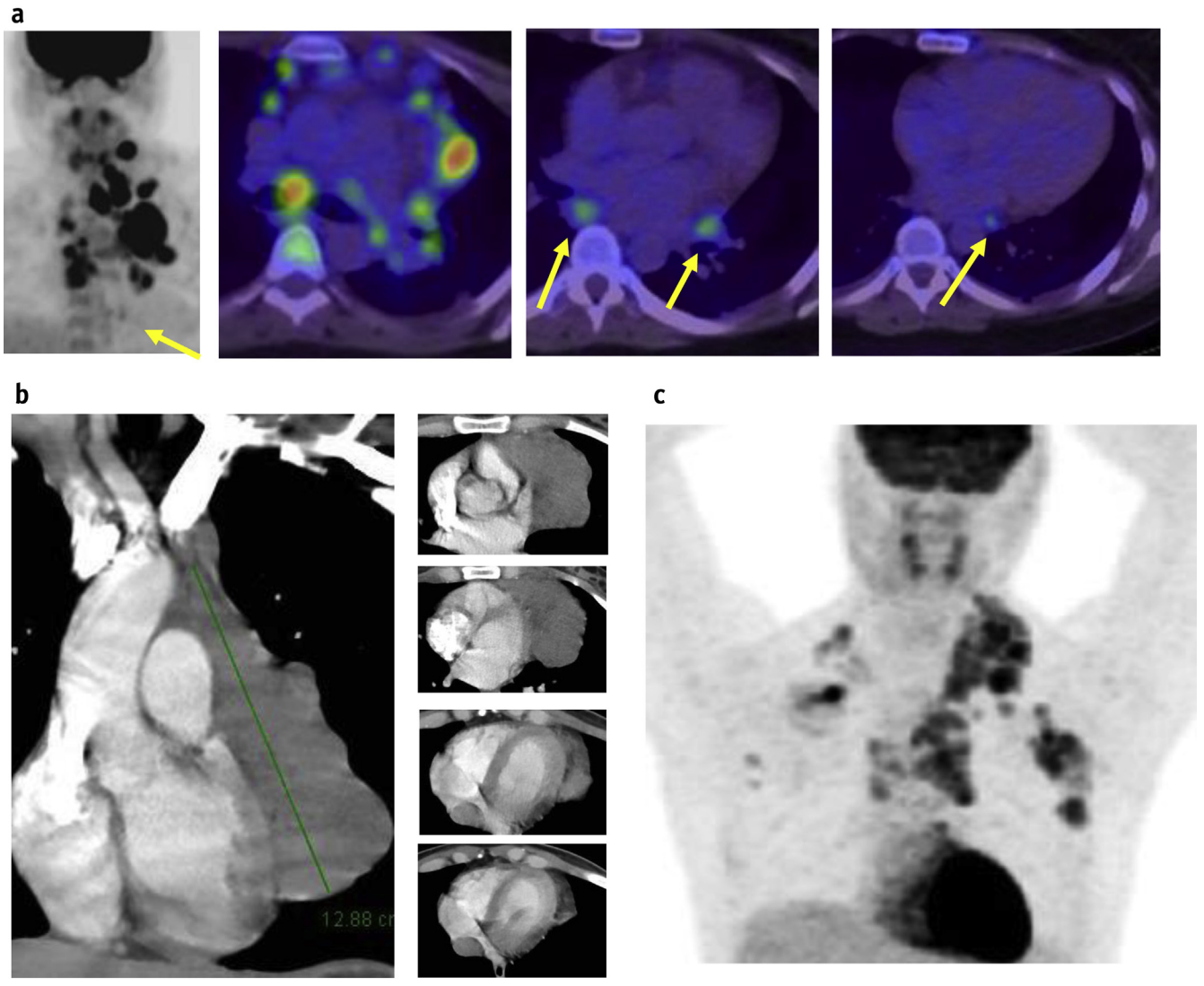


Fig. 9. Unfavorable mediastinal lymphoma: bulky site with (a) discrete pericardial deposits or (b) contiguous mass; (c) widespread evenly distributed disease.

ISRT volume may approximate an old-fashioned mantle field (Fig. 9c). In the absence of a bulky mass, or other features identifying a high-risk subsite, ISRT presents an "all or none" choice. If a standard ISRT volume presents a high toxicity risk, chemotherapy alone may be used.

Hodgkin Lymphoma

Key evidence

Six cycles of ABVD produce an approximately 90% 3- to 5-year PFS for patients with unfavorable ESHL who are interim PET negative.[3,90] Sites at elevated risk of relapse after systemic therapy may potentially be identified by initial disease bulk (although total tumor burden is also prognostic), slow response to systemic therapy, and the presence of a residual PET-negative mass.[90-97]

The incremental benefit of radiation after a full course of systemic therapy is not well quantified. In the EORTC H10 unfavorable cohort, there were more locoregional relapses after 6 ABVD alone than after combined modality therapy with 4 ABVD, supporting the use of consolidative RT in this setting.[3] Randomized studies in advanced-stage disease report small, nonstatistically significant increases in PFS with RT to initial bulky masses achieving PET CR.[98,99]

The use of modified ISRT gains some support from the observation that small-volume disease sites in early PET complete remission are often controlled by systemic therapy alone.[3,68,93] A small retrospective study of HL treated with chemotherapy suggested that small cardiophrenic nodes can

safely be omitted from the irradiated volume.[100] However, reports of relapses in unirradiated small-volume sites provide a note of caution.[25] There is uncertainty regarding the size and number of lesions, and the aggregate proportion of the initial tumor burden, that can be omitted from the ISRT volume without decreasing tumor control rates.

An alternative to omission of disease sites is the use of a lower RT dose. Doses of 15 to 24 Gy have been reported to be effective for initial small-volume sites in morphologic and metabolic complete response in other clinical settings.[70,101-103]

Volume

After 6 cycles of ABVD, the minimum ISRT volume should include residual PET-positive lesions and residual PET-negative masses (often corresponding to initial bulky sites; Fig. 10). If this minimum volume cannot be treated while respecting dose constraints, consider withholding RT.

The CTV should be enlarged to include slowly responding sites (ie, positive interim PET) and as great a proportion of initial small-volume disease sites as practicable, without exceeding dose constraints. Isolated, small-volume sites at a distance from the bulky site may be excluded from the CTV, if necessary, to respect normal tissue dose constraints. Alternatively, a single distant cardiophrenic node may sometimes be safely encompassed in a small separate field. If it is necessary to exclude the majority of the initial aggregate tumor burden to remain within acceptable dose constraints, consideration should be given to withholding RT.

The use of less than standard ISRT after 4 or fewer cycles of ABVD is not recommended.

Primary Mediastinal B-Cell Lymphoma

Key evidence

For primary mediastinal B-cell lymphoma, dose adjusted rituximab, etoposide, prednisolone, vincristine, cyclophosphamide, adriamycin appears to be highly effective as sole therapy, particularly for patients with a metabolic CR.[104-106] R-CHOP chemotherapy is commonly followed by RT, although the benefit of consolidative RT for patients in PET CR after chemotherapy is uncertain.[107] This question was addressed in the recently completed IELSG-37 trial, and results are awaited with interest.[108-110]

A bulky mass, slow response to systemic therapy, or a residual mass may predict a higher risk of relapse for DLBCL.[85,111-114] As with HL, the use of modified ISRT directed to high-risk sites is supported by the ability of systemic therapy to control small-volume disease sites in early PET complete remission.[76,115]

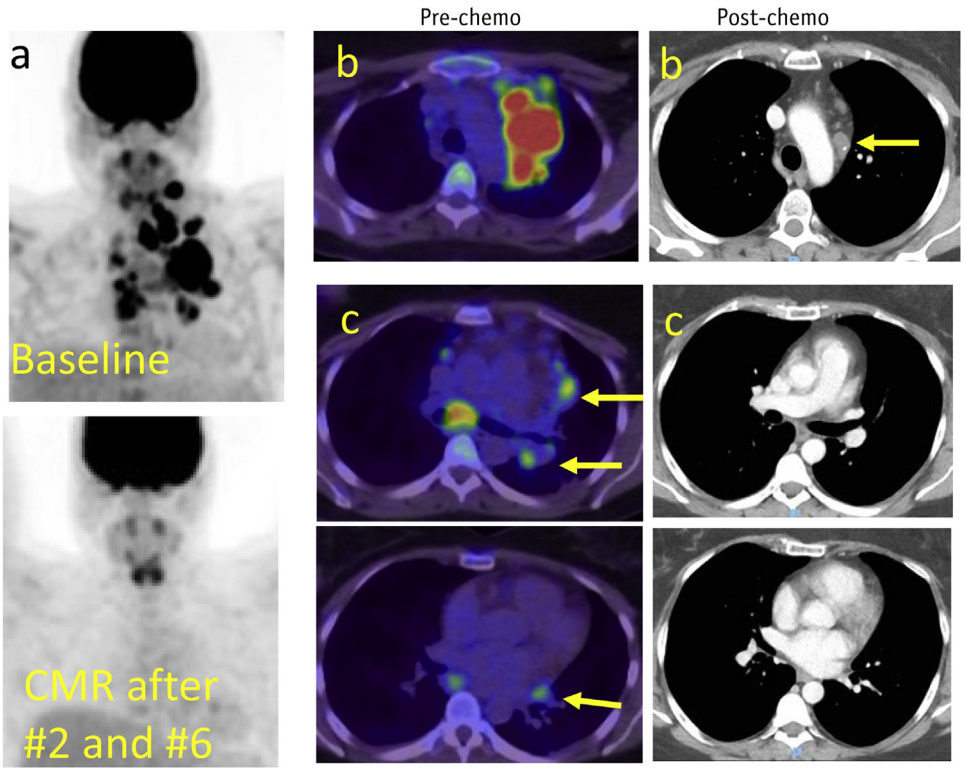


Fig. 10. Bulky early stage Hodgkin lymphoma in metabolic complete response after 6 ABVD: (a) pre- and post-chemotherapy positron emission tomography (PET); (b) initially bulky upper mediastinal disease with corresponding residual PET-negative mass; (c) small volume lower mediastinal and pericardial disease sites in structural and PET complete response. Consider irradiating upper mediastinal disease while omitting small-volume pericardial sites to minimize toxicity risk.

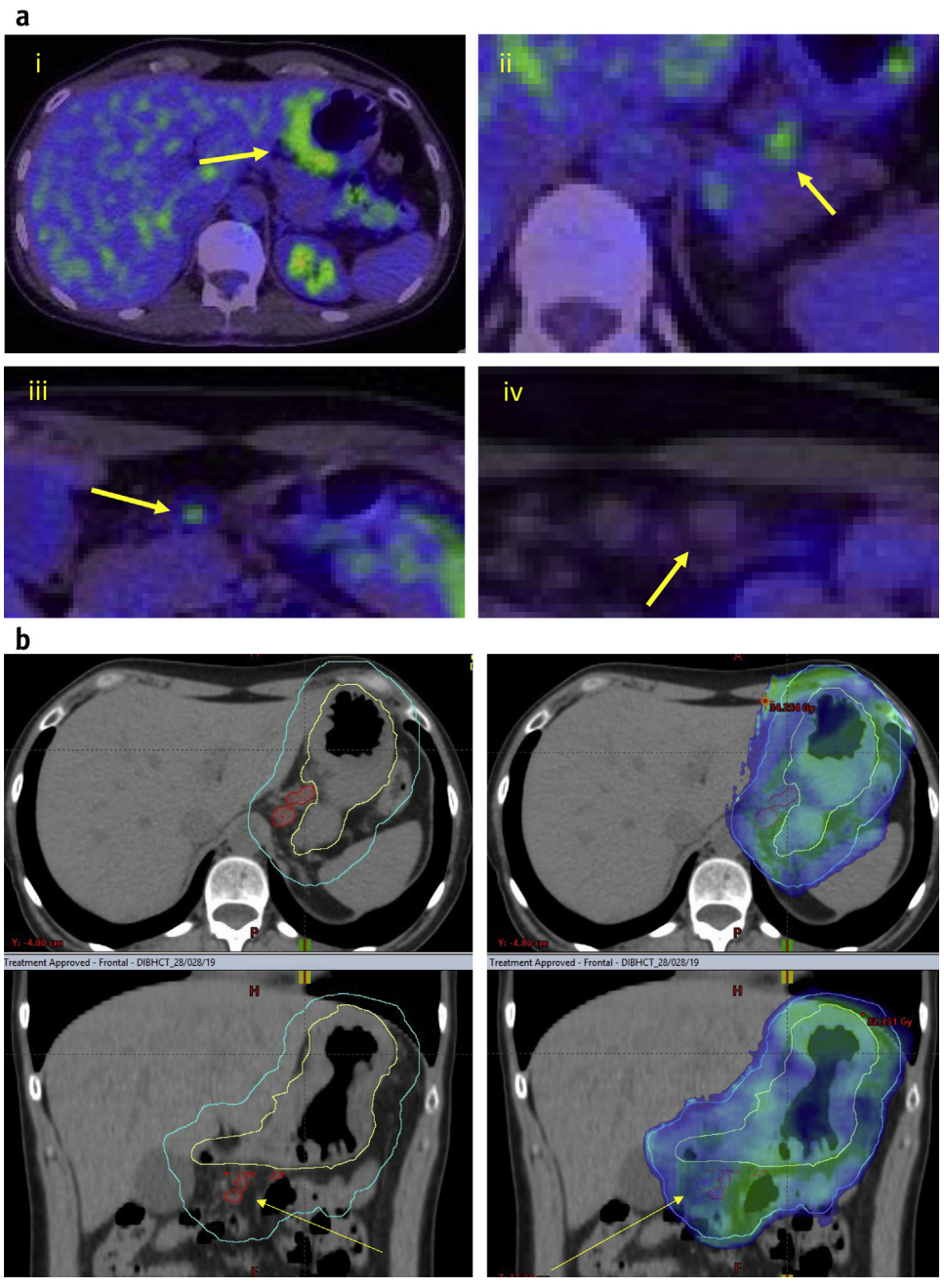


Fig. 11. Gastric marginal zone lymphoma with nodal involvement: (a) arrows indicate (i) gastric wall involvement, (ii, iii) nodal uptake on positron emission tomography, (iv) enlarged positron emission tomography negative node; (b) clinical target volume (CTV) including whole stomach (yellow) and suspicious adjacent nodes (red), planning target volume (blue), and intensity modulated radiation therapy plan. (c) Note the greater distance from CTV to heart and breast tissue in breath hold. (d) Cone beam computed tomography showing variation in stomach shape and position (CTV in yellow). (A color version of this figure is available at https://doi.org/10.1016/j.ijrobp.2020.03.019.)

ISRT for Primary Extranodal Lymphoma

Overview

Primary extranodal lymphomas present great anatomic and biological variety. They may be multifocal within organs (macro- or microscopically); may track along organ walls, cavities, and tissue planes; and may be subject to organ motion and deformability, leading to uncertainty in determining optimal CTV, ITV, and PTV expansions.[11] Two common categories, MZL and DLBCL, are discussed below. Readers are referred to previous publications for reviews of cutaneous lymphomas, nasal NK/T-cell lymphoma, and other rare extranodal subtypes.[7,11,116]

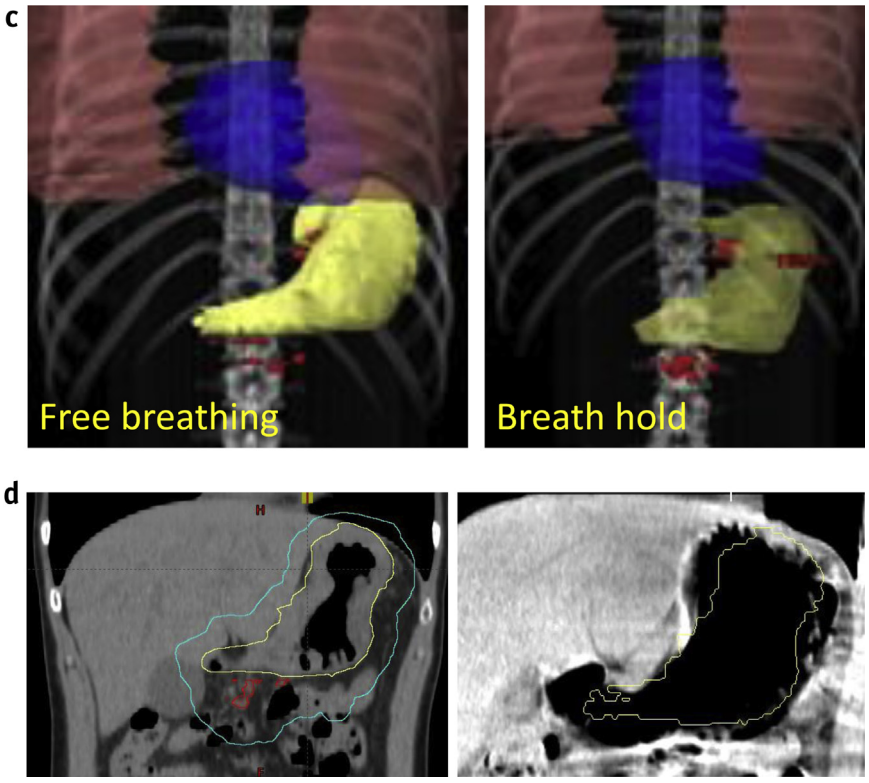


Fig. 11. (*Continued*).

Localized Extranodal MZL

Key evidence

For MZL, most published data reflect the results of whole organ irradiation (eg, stomach, salivary glands, thyroid), which is the default approach.[58,59] For conjunctival MZL, irradiation confined to the conjunctival sac is highly effective.[11,117] For MZL of the lacrimal gland, recent data suggest that treatment may be confined to the lacrimal gland, treating it as a separate organ rather than as part of the "orbital adnexae" (as done historically). There are conflicting data on the efficacy of this approach.[118,119]

Volume

The GTV includes PET-positive lesions and PET-positive adjacent or regional nodes. Supplementary information from CT, MRI, ultrasound, and endoscopy are especially important for defining the GTV for MZL considering its low FDG avidity.

The CTV usually includes the entire involved organ or compartment: for example, for gastric MZL the whole stomach is irradiated (Fig. 11). Equivocally involved adjacent lymph nodes should be included in the CTV. For MZL limited to the conjunctiva, the entire conjunctival sac is irradiated with no need to irradiate the whole orbit (Fig. 12). Partial orbital irradiation may be considered for MZL of the lacrimal gland with no evidence of disease beyond the gland on MRI. Partial organ irradiation may be considered in other settings where whole organ irradiation is not feasible or potentially toxic (ie, lung, skin, breast in young women) on an individual case basis. Image guidance, motion management, and adequate ITV/PTV expansions must be used to account for organ motion and deformability (Fig. 11c, 11d).

Dose

Currently, 24 to 30 Gy is standard for MZL, with 24 Gy commonly used for sensitive sites such as the orbit.[59,67,117,120,121] A dose of 4 Gy provides durable local control in about two-thirds of patients (although less effective than 24 Gy in a randomized trial) and is being evaluated for MZL in prospective trials.[66,122] A strategy of using 4 Gy and reserving higher doses for patients not achieving CR is a very attractive, low-toxicity approach for sensitive anatomic sites and for patients who are elderly or at higher than average toxicity risk.

Primary Extranodal DLBCL after 3 to 6 Cycles of Systemic Therapy

Key evidence

For most primary sites, optimal irradiated volumes have not been defined in prospective trials. Whole organ irradiation is the most widely reported approach for many sites (eg,

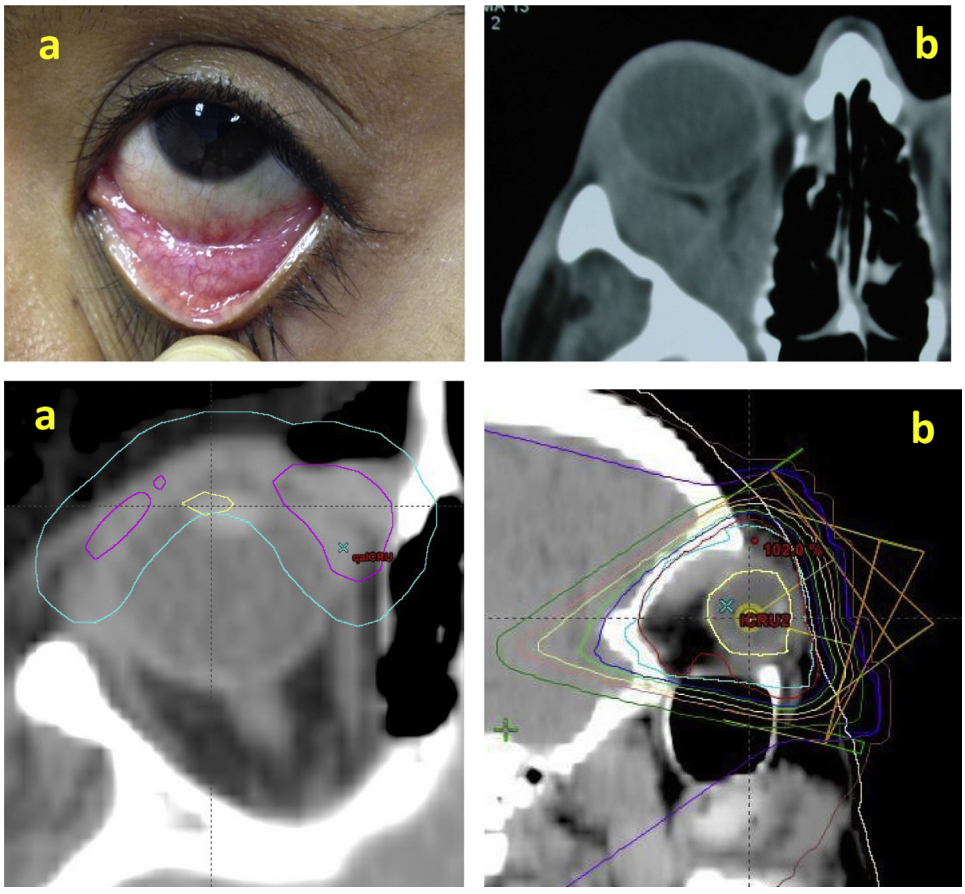


Fig. 12. Marginal zone lymphoma of the orbit. (a) Conjunctival disease, with clinical target volume (CTV) limited to the conjunctival sac. (b) Posterior orbital soft tissue mass with CTV including whole orbit.

stomach, thyroid, breast) and is mandatory for sites in which disease is usually multifocal (eg, primary CNS lymphoma).[123]

The limitations of imaging in detecting small-volume disease extensions, together with organ motion and deformation, make partial organ irradiation risky in many anatomic locations. Partial organ irradiation is appropriate for unifocal DLBCL involving long bones when disease extent is well defined on baseline PET and MRI. For DLBCL of lung and skin, RT is confined to the tissue volume involved before systemic therapy. Partial organ irradiation may be considered in selected cases of breast lymphoma to minimize toxicity risk (Fig. 13).[123]

Volume

For most primary sites, the CTV includes the whole organ/compartment.

For partial organ irradiation, the CTV includes pre-chemotherapy involved tissue volume seen on baseline PET supplemented by CT, MRI, ultrasonography, endoscopy, or clinical findings, as appropriate. In addition, the limitations of imaging for some extranodal sites may warrant an expansion to allow for contouring uncertainties.

In special cases prophylactic irradiation of potential microscopic disease is indicated when there may be a degree of chemoresistance or limited drug access to the volume at risk.[11] For example, for testis lymphoma the CTV includes the scrotum with contralateral testis.[124]

Dose

The recommended dose is 30 to 36 Gy.

ISRT after Full-Dose Systemic Treatment for Advanced-Stage Aggressive NHL/HL

Overview

There is a lack of uniform practice regarding the use of RT (and treatment volume) for patients with advanced-stage lymphomas. After a full course of systemic therapy, RT is considered for sites potentially at elevated risk of relapse, such as initially bulky sites. The use of RT is influenced by the anticipated toxicity of the requisite field and the potential for salvage therapy should the patient relapse.[125-127]

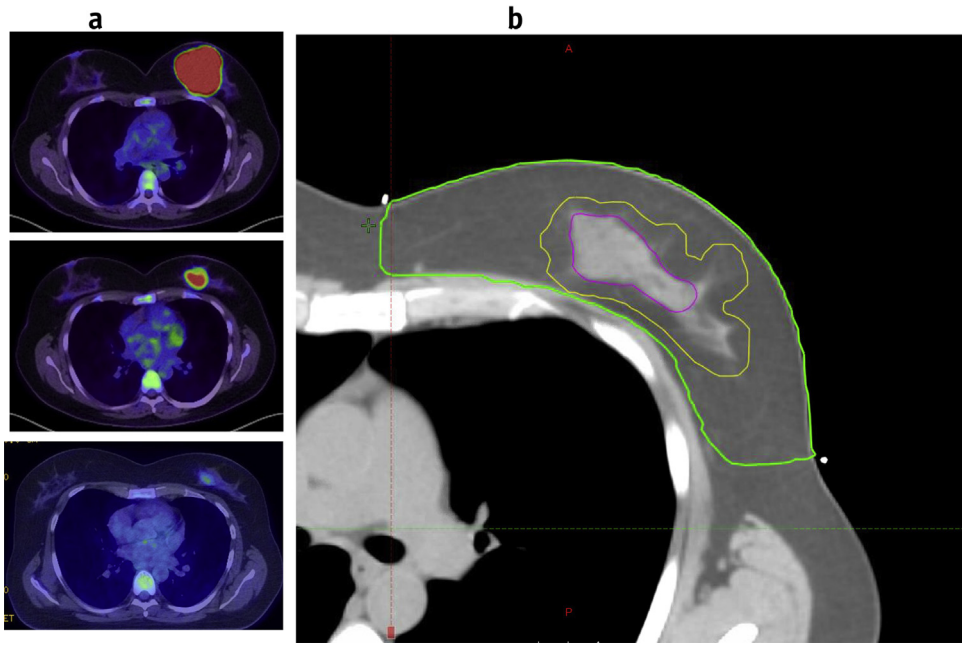


Fig. 13. (a) Primary breast diffuse large B-cell lymphoma with positive interim positron emission tomography and metabolic complete response after 6 cycles of R-CHOP; (b) clinical target volume options include residual mass corresponding to the initial fluorodeoxyglucose-avid location adjusted for shrinkage (red), contiguous soft tissue density (yellow), or the entire breast (green). In this case, the positive interim positron emission tomography led to a more intensive approach, with whole breast treated to 30 Gy and residual mass treated to 36 Gy. (A color version of this figure is available at https://doi.org/10.1016/j.ijrobp.2020.03.019.)

Advanced DLBCL

Key evidence

The risk of relapse for DLBCL after 6 cycles of R-CHOP reflects the International Prognostic Index, the initial tumor bulk (usually defined as a mass >7.5 cm), the rapidity and completeness of metabolic response, and the presence of a PET-negative residual mass. The relationship between these factors and the pattern of failure has not been well studied. RT may reduce the risk of relapse when given to sites of initial disease bulk, and potentially to sites exhibiting slow metabolic response and PET negative residual masses.[84,85,111,113,126-132] RT alone may salvage a proportion of patients with a residual PET-positive site.[133]

Volume

For patients in PET CR, the CTV may include residual masses (usually corresponding to initially bulky sites) as well as adjacent, initially involved nodes that have normalized after chemotherapy to minimize the risk of a marginal relapse (Fig. 14). This may be influenced by the bulk of initially involved adjacent sites and the impact of a larger CTV on potential toxicity.

Residual FDG-positive sites constitute the "postchemo" GTV. If the PET-positive lesion constitutes part of a residual mass on CT, the PET-negative residuum should be included (Fig. 15).

Dose

After PET CR, 30 to 36 Gy is recommended.[14,67,84,85,115,129] PET-positive residual masses should receive 36 to 50 Gy.

Advanced HL

Key evidence

After ABVD chemotherapy

Historically, adjuvant RT did not benefit patients with advanced-stage HL in CR on structural imaging after 6 cycles of mechlorethamine, vincristine, procarbazine, prednisolone, adriamycin, bleomycin, vinblastine (MOPP-ABV), but it appeared beneficial for patients with residual masses.[134,135] In the PET era, the RATHL trial did not evaluate RT but failed to demonstrate an adverse impact of bulky disease for patients who had a negative interim PET scan.[90] In 2 recent Italian trials (GITIL 0607 and FIL HD0801), consolidative RT to bulky sites (>5 cm) in PET CR after ABVD chemotherapy was associated with non-statistically significant increases in PFS of 4% and 7.5% (intention-to-treat analysis), respectively.[98,99] Rapidity of metabolic response has been used to guide RT use in pediatric patient trials, and a recent analysis of SWOG S0816

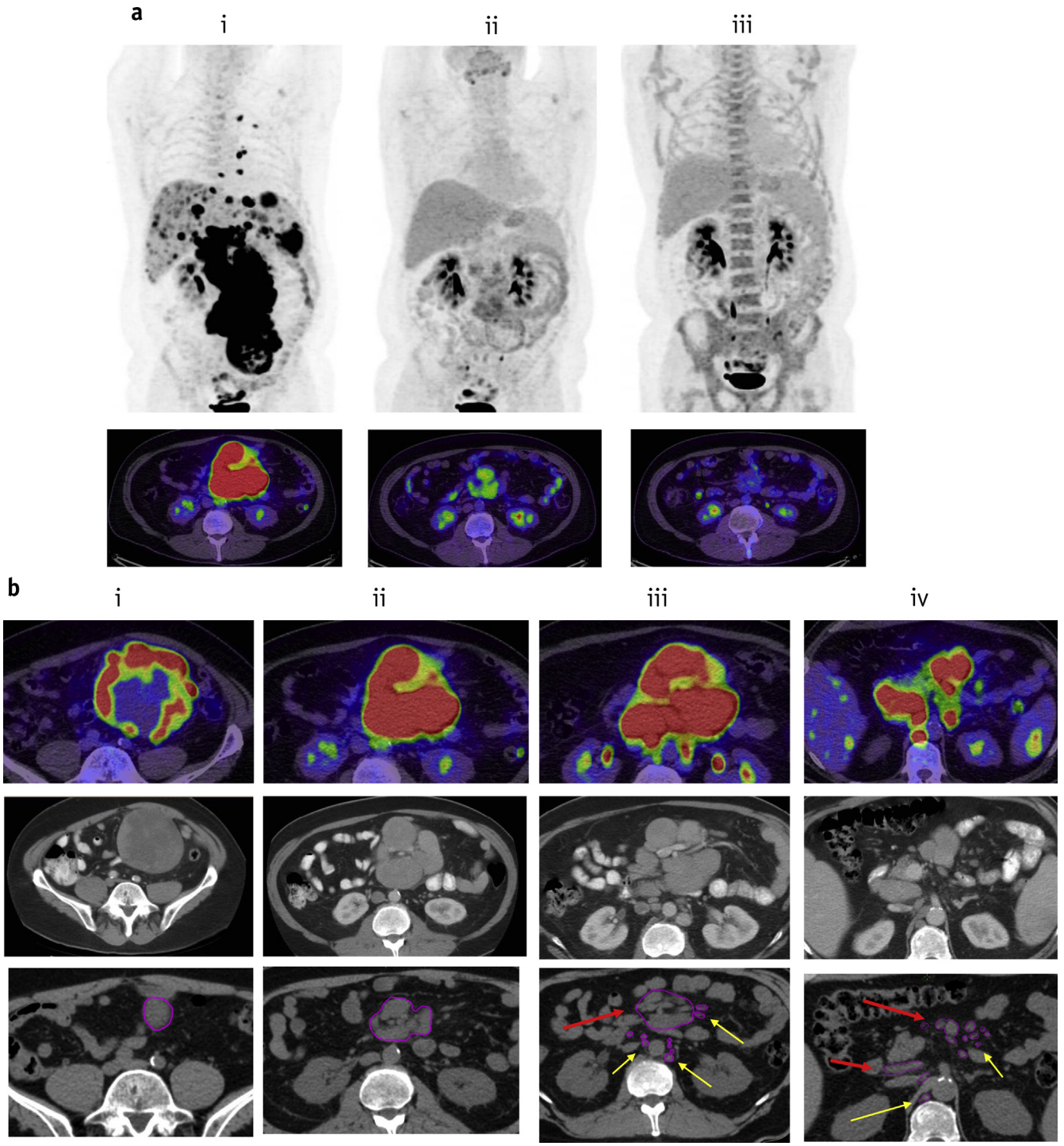


Fig. 14. (a) Stage IV diffuse large B-cell lymphoma, with bulky abdominal mass (i); partial response on interim positron emission tomography (ii); complete response after 6 cycles of R-CHOP (iii). The initially bulky mass was irradiated; (b) the clinical target volume (CTV) (pink) includes posttreatment residua, corresponding to the initial mass (i, ii); initial conglomerate mass resolved into clusters of enlarged and normal-sized residual nodes post-chemotherapy (iii, iv). CTV included enlarged (red arrows) and normal-sized residual nodes (yellow arrows). (A color version of this figure is available at https://doi.org/10.1016/j.ijrobp.2020.03.019.)

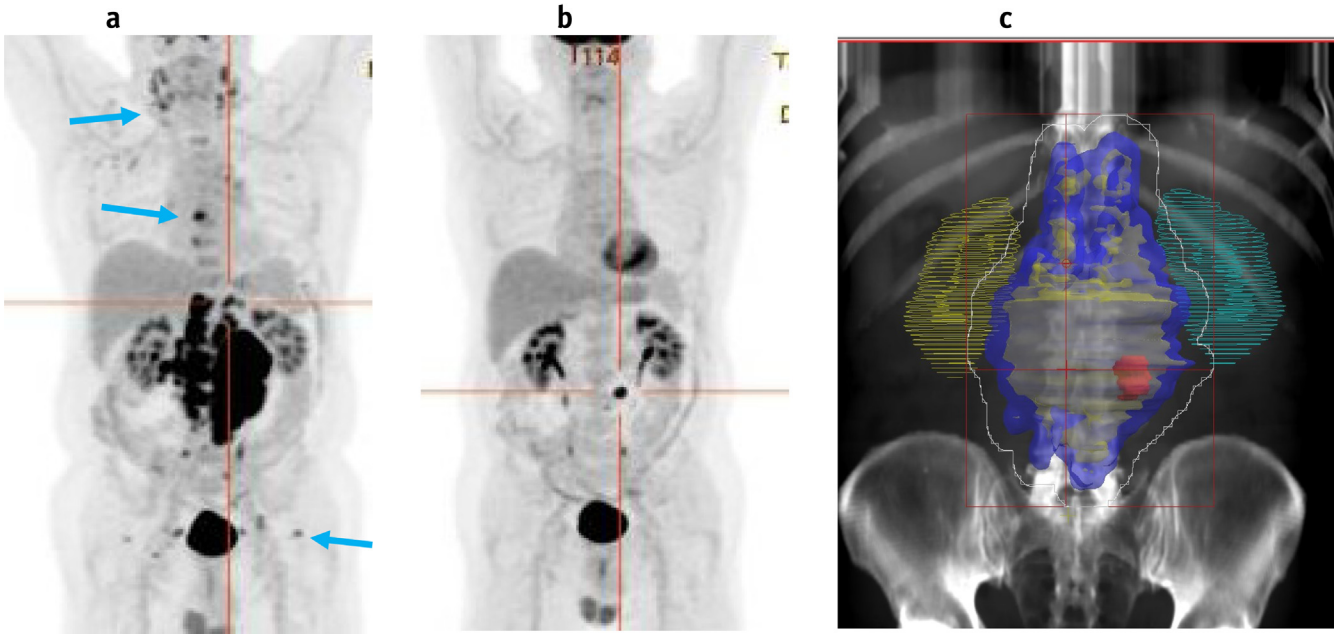


Fig. 15. Stage III diffuse large B-cell lymphoma treated with 6 cycles of R-CHOP: (a) baseline bulky mesenteric mass and small-volume distant nodes (blue arrows); (b) residual positron emission tomography−positive node postchemotherapy; (c) involved site radiation therapy options include residual positron emission tomography−positive mass (in red) only; initially involved nodes that remained enlarged on computed tomography (in gray); slightly larger volume encompassing all contiguous initially involved nodes (blue). Inclusion of the initial bulky disease is recommended, with modifications for toxicity considerations. (A color version of this figure is available at https://doi.org/10.1016/j.ijrobp.2020.03.019.)

suggests that interim PET may guide the use of consolidative RT.[136,137] This is supported by an unplanned analysis of the UK RATHL trial, suggesting a benefit from RT for patients with positive interim PET.[97] In current practice, the use of RT after ABVD for advanced stage HL is highly selective, based on tumor bulk, response, and disease distribution.

After BEACOPP chemotherapy

After esc-BEACOPP, RT is effective for patients with residual FDG-avid masses ≥2.5 cm in largest diameter.[138,139] An adequate ISRT volume should include the contiguous non-FDG−avid soft tissue mass.[48,138]

Volume

On occasions when RT is given after ABVD chemotherapy, the CTV includes residual PET-negative masses generally corresponding to initially bulky sites.

Residual PET-positive sites after ABVD or BEACOPP constitute the GTV. If the PET-positive lesion is part of a residual mass, the contiguous PET-negative residuum should be included in the GTV (Fig. 16).

Dose

For sites in metabolic CR, 30 Gy is standard. Residual PET-positive masses are treated to 36 to 45 Gy.[15]

ISRT for Relapsed/Refractory Aggressive NHL or HL

Overview

RT is commonly a component of salvage therapy with systemic treatment, including autologous stem cell transplantation.[8,10] RT has an evolving role with new biologic/immunologic therapies, as bridging therapy (including to chimeric antigen receptor T cell therapy), as an "immunostimulant," or for definitive local treatment.[140] Salvage RT may be the sole therapy for limited extent relapse and for patients who are unable to tolerate aggressive systemic therapy.[141] Salvage strategies are influenced by disease stage at diagnosis and at relapse/progression, time to first relapse, histology, and patient fitness for aggressive therapy. The use of salvage RT requires multidisciplinary discussion and individualized patient management and is discussed in detail in recent ILROG publications.[8,10]

Volume

In salvage settings, tumor control may be prioritized over toxicity minimization, with potentially larger ISRT volumes.

Limited disease extent at relapse

A relapse of limited anatomic extent may sometimes be entirely encompassed within a tolerable treatment volume.

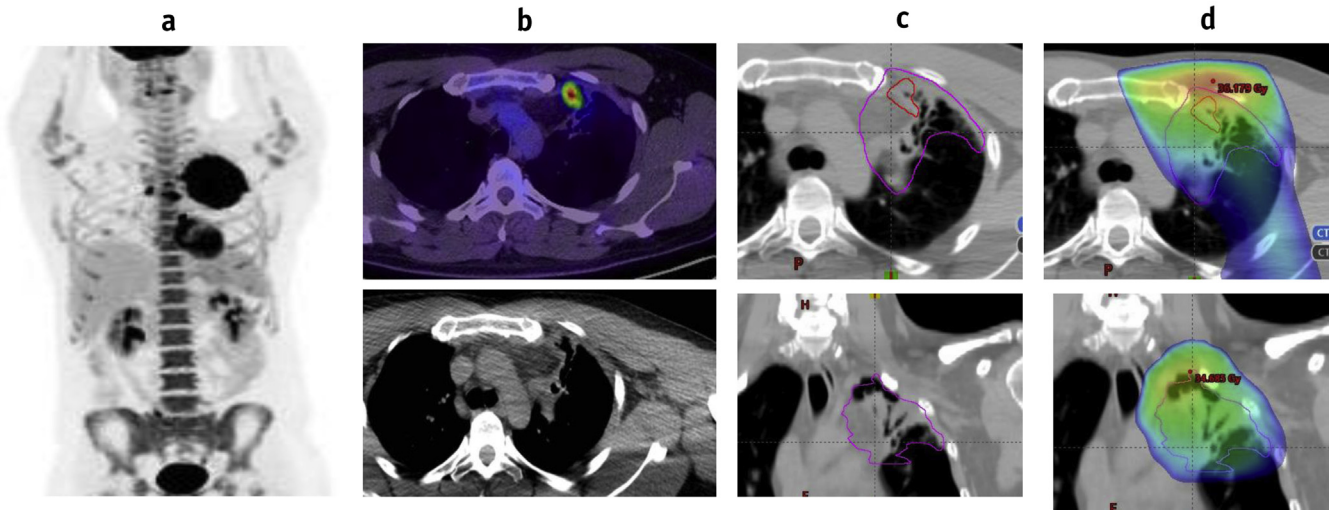


Fig. 16. Bulky stage IIBE (lung) Hodgkin lymphoma with residual positron emission tomography (PET) positive lesion after 6 cycles of esc-BEACOPP: (a) baseline PET; (b) postchemotherapy PET and computed tomography showing residual PET-positive lesion and surrounding soft tissue mass; (c) involved site radiation therapy volume with gross tumor volume (red) encompassing residual PET-positive lesion and encompassing adjacent PET-negative residuum (pink); (d) treatment plan. (A color version of this figure is available at https://doi.org/10.1016/j.ijrobp.2020.03.019.)

In such cases, the CTV may include all relapse sites, including sites in CR after systemic therapy. Equivocal nodes adjacent to definite relapse sites should generally be included in the CTV. If relapse sites are close to sites at initial diagnosis, consideration may be given to including the original disease extent in the CTV (Figs. 17, 18). This is particularly the case with primary treatment failure or early relapse because a degree of chemoresistance is assumed, with a consequent higher likelihood of progression within previously involved sites.[142]

Sites of active disease after systemic salvage therapy (or if no systemic therapy is given) constitute the GTV.

Widespread relapse

It is usually not feasible to encompass widespread disease sites in a tolerable ISRT volume. It may be possible to identify sites at elevated risk of relapse after systemic salvage therapy, based on bulk at relapse and rapidity and completeness of response to systemic salvage therapy.[3,5] For patients undergoing autologous transplantation, response to cytoreduction therapy may predict relapse risk.[142]

Sites of residual PET-positive disease after systemic therapy constitute the GTV. PET-negative sites at potentially increased risk of relapse, as well as clinically critical sites (eg, spinal cord compression, proximal airway compression), may be considered for inclusion in a CTV.

Dose

For patients in metabolic CR after salvage chemotherapy and autologous stem cell transplantation, 30 Gy for HL and 30 to 36 Gy for DLBCL are recommended. Higher doses may be considered for bulky relapse sites, FDG-avid sites after pretransplant cytoreductive systemic therapy, or residual posttransplant masses.

For residual disease after systemic therapy (or if RT is the sole salvage therapy) the dose to the GTV is 36 to 45 Gy for HL and 40 to 55 Gy for DLBCL.

Conclusions and Future Directions

The application of ISRT varies across the lymphoma clinical spectrum and according to the quality and applicability of available imaging. Emerging data on patterns of failure after standard treatment will likely influence the application of ISRT in the future. For example, the demonstrated efficacy of immunotherapy or immunochemotherapy for control of systemic disease in follicular lymphoma may provide increasing confidence in the use of smaller CTV margins in the future.[65,143] For patients with ESHL, ongoing research is evaluating whether RT can be limited to residual anatomic abnormalities after systemic therapy (or omitted in selected patients).[144] If this proves to be the case, patients may be able to receive effective consolidative RT with potentially lower morbidity risk, particularly for patients with initially extensive mediastinal lymphoma.[32] As systemic therapy evolves, particularly with the development of new immunotherapies, our approach to defining ISRT will also certainly evolve.

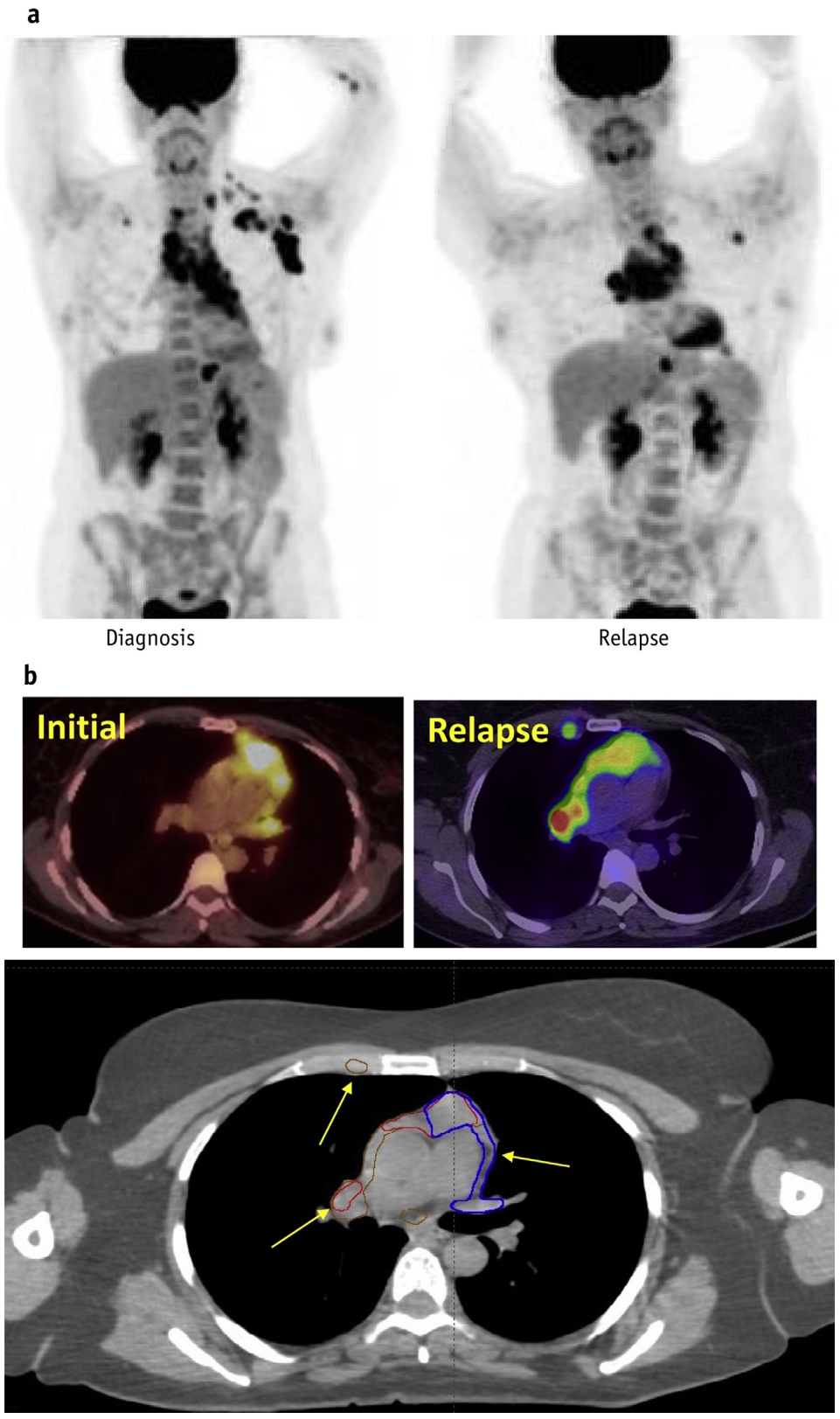


Fig. 17. Stage II Hodgkin lymphoma with relapse after 6 cycles of ABVD, for posttransplant involved site radiation therapy: (a, b) different disease distributions at diagnosis and relapse shown on positron emission tomography and planning computed tomography; (c) digitally reconstructed radiograph showing initial (pink) and relapse sites (blue). (d) Treatment plan delivering 30 Gy volume to all relapse sites (i). A dose of 20 Gy was given to previously involved sites to reduce coronary and myocardial exposure (ii). Isolated cardiophrenic node treated with separate electron beam (arrow; iii). (A color version of this figure is available at https://doi.org/10.1016/j.ijrobp.2020.03.019.)

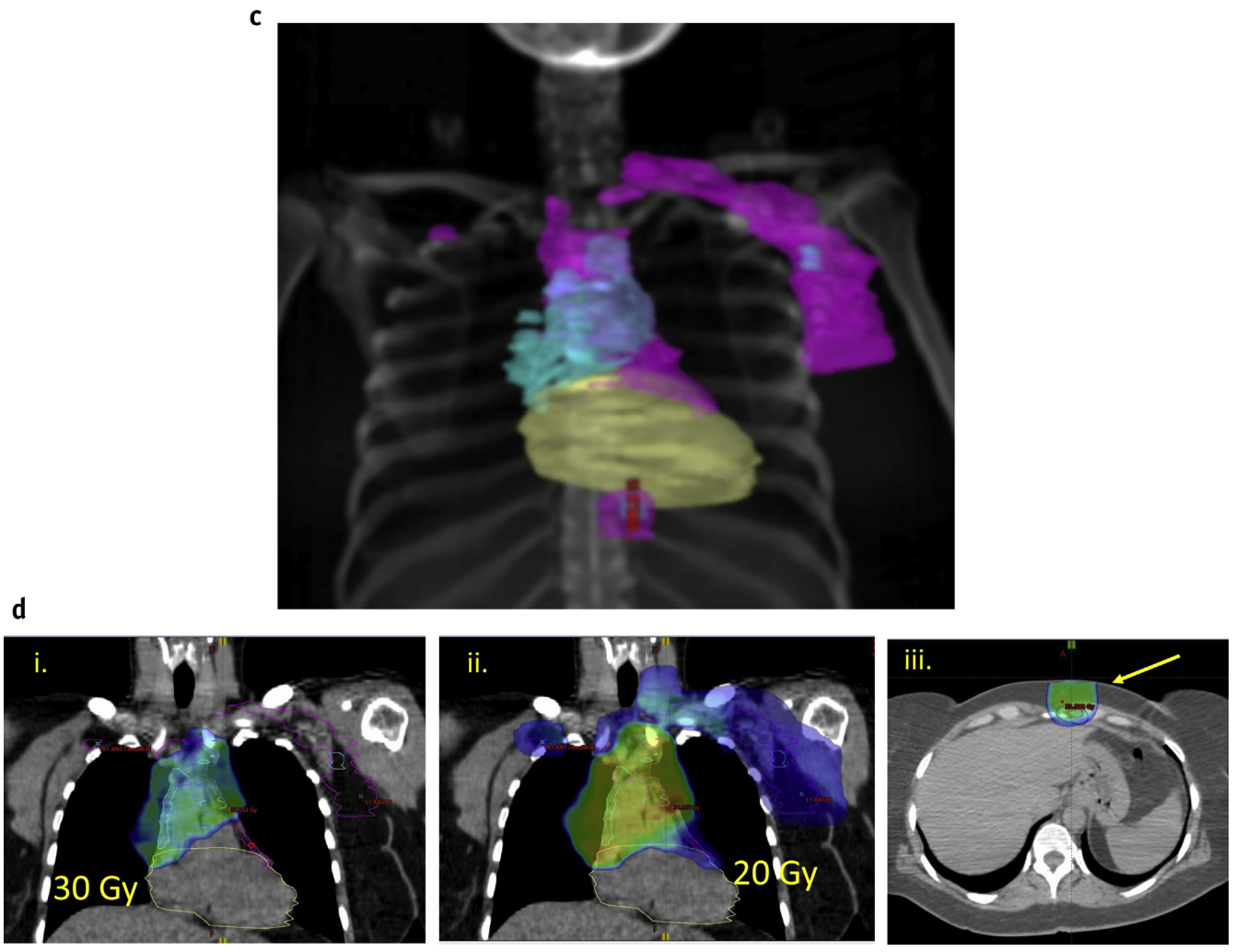


Fig. 17. (*Continued*).

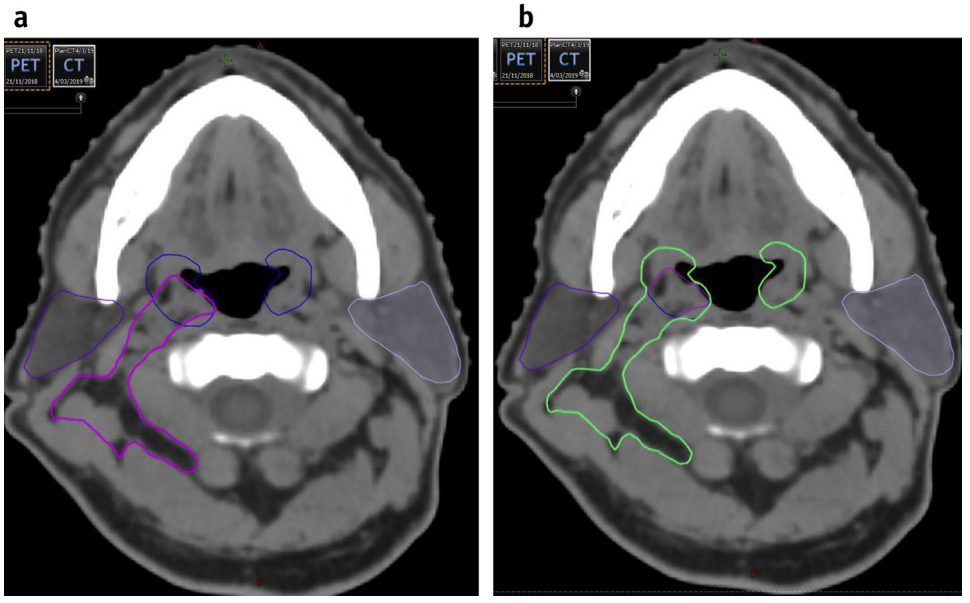


Fig. 18. Relapsed diffuse large B-cell lymphoma for posttransplant radiation therapy: (a) initial tonsillar involvement (blue) with contiguous/overlapping relapse sites (pink); (b) clinical target volume incorporating both volumes. (A color version of this figure is available at https://doi.org/10.1016/j.ijrobp.2020.03.019.)

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